in KCNQ1 (representing 10% of allKCNQ1 mutations). In addition, 4 nonsense mutations were found in KCNH2, whereas only 1 in KCNQ1 and none in SCN5A.
Conclusions: The present study shows that average QTc, Schwartz score,episodes of syncopeare associated with a higher detection rate of mutations in LQTS among Chinese patients. In addition, our study indicates that the majority mutations harbored by LQTS patients are on LQT1-3 causing genes and LQT2 is the most common subtype in Chinese patients. The present study also expands the spectrum of LQTS-causing mutations in Chinese.

For Chinese Channelopathy Register Investigators

GW25-e4615

Renal denervation suppresses atrial fibrillation in a model of renal impairment

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Objectives: A close association exists between chronic kidney disease (CKD) and atrial fibrillation (AF) occurrence. Activation and overactivity of sympathetic nervous system (SNS) may be one of the pathogenic mechanisms responsible for the development of AF associated with renal impairment (RI). Renal denervation (RDN) decreases sympathetic renal afferent nerve activity, leading to decreased central sympathetic drive.The main objective of the study was to explore the effects of SNS and RDN on AF inducibility in anesthetized beagles with RI.
Methods: Unilateral RI was induced in beagles by embolization of small branches of the renal artery in the left kidney using gelatin sponge granules in RI (n=6) and RI+RDN group (n=6). The control group (n=6) underwent the same procedure, except for embolization. Then animals in RI+RDN group underwent radiofrequency ablation of the renal sympathetic nerve. Cardiac electrophysiological parameters, blood pressure (BP), AF inducibility, plasma norepinephrine, renin and aldosterone were measured at baseline and after 2 weeks. Levels of angiotensin II, aldosterone, transforming growth factor-β (TGF-β) and fibrosis in atrial tissue were measured after 2 weeks.
Results: We observed 5 main findings. (1) Embolization of small branches of the renal artery in the left kidney led to ischemic RI with mild renal insufficiency. (2) Heart rate and BP were elevated by RI, which were reversed by RDN. (3) Atrial effective refractory period was shortened and AF inducibility was increased by RI, which were reversed by RDN. (4) Antegrade Wenckebach point was shortened and ventricular rate during AF was increased by RI, which were reversed by RDN. (5) Plasma norepinephrine level was elevated by RI, levels of renin and aldosterone in plasma, angiotensin II aldosterone, TGF-β and fibrosis in atrial tissue were elevated by RI, which were reversed by RDN.
Conclusions: RDN significantly reduced AF inducibility, reversed the atrial electrophysiological changes and inhibited fibrotic pathway in a model of RI by combined reduction of sympathetic drive and renin-angiotensin-aldosterone system activity.

GW25-e5127

The role of PDE5 in resveratrol-induced cardioprotection against ischemia/reperfusion injury

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Objectives: Resveratrol has been established to be cardioprotective and our previous study demonstrated that resveratrol prevents cardiac reperfusion injury by targeting the mitochondrial permeability transition pore (mPTP) through inactivation of GSK-3β via the cGMP/PKG signaling pathway. Nevertheless, the exact mechanism by which resveratrol activates the cGMP/PKG pathway remains unclear. The intracellular cGMP level is regulated by both guanylyl cyclase that promotes the synthesis of cGMP using NO and phosphodiesterase (PDE) that induces the hydrolysis of cGMP. The purpose of this study was to explore the molecular mechanism by which resveratrol increases intracellular cGMP leading cardioprotection against reperfusion injury, focusing on the roles of NO and PDE5.
Methods: Rat cardiomyocytes were isolated enzymatically. Fluorescence dye 4-amino-5-methylamino-2', 7'-difluorofluorescein (DAF-FM) was used to image NO. Fluorescence images were obtained with confocal microscopy. Isolated rat hearts were subjected to 30 min regional ischemia followed by 2 h of reperfusion. Myocardial samples were collected from the risk zone for PDE5 activity, cGMP levels, and western blot analysis. Infarct size was measured by TTC staining. Mitochondrial swelling was measured spectrophotometrically as a decrease in absorbance at 520 nm (A520).
Results: Cardiomyocytes treated with resveratrol for 10 min did not show a significant increase in DAF-FM fluorescence intensity, indicating that resveratrol does not produce NO. In contrast, resveratrol significantly reduced PDE5 activity and increased cGMP levels at reperfusion in the heart, indicating that the cardioprotective effect of resveratrol is not mediated by guanylyl cyclase but is dependent on PDE5. The non-selective PDE inhibitor 3-isobutyl-1-methylxanthine (IBMX) could mimic the cardioprotective effect of resveratrol by reducing infarct size through modulation of the mPTP opening. In addition, resveratrol enhanced the phosphorylation of VASP and GSK-3β, an effect that was partially blocked by PKG inhibitor KT5823.
Conclusions: Inhibition of PDE5 leading to the increase in intracellular cGMP accounts for the cardioprotective effect of resveratrol on reperfusion injury through prevention of the mPTP opening via the cGMP/PKG/GSK-3β signal pathway.

GW25-e5194

A protective role of SIRT3 in endothelial function under metabolic stress

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Objectives: Recent evidence has shown that loss of SIRT3 contributes to the development of the metabolic syndrome but the role of SIRT3 in endothelium dysfunction under metabolic stress has not been identified.
Methods: Male SIRT3 KO and age-matched wide type mice were fed with standard chow diet or high fat diet (HFD) for 24 weeks. The vasoactive responses to phenylephrine, sodium nitroprusside and acetylcholine and ROS production in isolated thoracic aortic segments were determined.
Results: Phenylephrine, sodium nitroprusside, and acetylcholine evoked similar vascular responses in SIRT3 KO and wild type mice fed with standard chow diet. However, compared with the wild type fed with HFD, endothelium-dependent relaxation to acetylcholine was impaired in SIRT3 KO mice fed with HFD. Furthermore, SIRT3 KO mice fed with HFD displayed decreased NO bioavailability and increased mitochondrial superoxide formation compared with the wild control fed with HFD. In human endothelial cells, SIRT3 knockdown exacerbated mitochondrial ROS production while SIRT3 overexpression protected endothelial function against palmitate treatment.
Conclusions: Our data have shown that SIRT3 deficiency increases mitochondrial ROS production and exacerbates endothelium dysfunction in mice fed with high-fat diet, indicating a protective role in endothelial homeostasis under metabolic stress.

GW25-e5236

Rosuvastatin Attenuates Lps-Induced Adhesion Molecules Expression in Human Umbilical Vein Endothelial Cells

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Objectives: Stable adhesion and transendothelial migration of leukocytes into the vascular wall play an important role in atherogenesis. Cell adhesion molecules such as intracellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) mainly mediates in this process. We investigated the effect of rosuvastatin, an inhibitor of HMG-CoA reductase administered to reduce plasma levels of LDLcholesterol, on the expression of VCAM-1 and ICAM-1 by human umbilical vein endothelial cells (HUVEC) stimulated with lipopolysaccharide (LPS).
Methods: The HUVECs were primary cultured. HUVECs from the second to fourth generations were stimulated with different concentrations of LPS and the model of cell injury was set up. Then the HUVECs were pretreated with rosuvastatin in different concentration for 2 hours before LPS is added. The expression of VCAM-1 mRNA and ICAM-1 mRNA was evaluated by real time-PCR. The content of VCAM-1 protein and ICAM-1 protein was detected with western blot. mevalonate (MEV) was added to evaluate whether the effect of rosuvastatin on expression of VCAM-1 and ICAM-1 protein can be blocked.
Results: We found the expression of cell adhesion molecules to be significantly inhibited by the rosuvastatin in a time and concentration-dependent manner and to a greater extent in the case of VCAM-1 as compared with ICAM-1. The content of VCAM-1 protein and mRNA, ICAM-1 protein and mRNA significantly decreased when pretreated with certain concentration of rosuvastatin ($P<0{\cdot}05$). The effects of rosuvastatin on VCAM-1 and ICAM-1 protein can't be blocked by mevalonate. Rosuvastatin inhibited LPS-induced activation of nuclear factorκB (NF-κB).
Conclusions: The findings suggest that the benefits of rosuvastatin in vascular disease may include the inhibition of expression of VCAM-1 and ICAM-1 through effects on NF-κB, and the effect is independent on its lipid-lowering effect.

GW25-e5238

Lycopene protects endoplasmic reticulum stress induced apoptosis against neonatal mouse cardiomyocytes hypoxia/reoxygenation injury

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Objectives: Endoplasmic reticulum (ER) stress induced apoptosis has been implicated as a critical cause in the pathogenesis of myocardial ischemia reperfusion (I/R) injury. Our previous studies demonstrated that lycopene exhibits great pharmacological potential in protecting against the I/R-injury, but whether its effect is mediated through attenuation of ER stress-induced apoptosis remains unclear. The aim of this study was to investigate the effect of lycopene on hypoxia/reoxgenation (H/R) induced ER stress in primary cultured neonatal mouse cardiomyocytes.
Methods: Primary cardiomyocytes were isolated from neonatal C57BL/6 mice and divided into four groups: control, lycopene, H/R, lycopene + H/R. The cultured cardiomyocytes underwent 4h of hypoxia followed by 6h of reoxgenation to achieve H/R model. Cardiomyocytes were pretreated with lycopene (5 μM) prior to H/R treatment in lycopene + H/R. Cell viability was assessed using CCK-8 assay in each